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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/014,099	11/12/2001	Ralf Kuhn	100725-21/Kreisler 1097-K	2636
27384	7590	11/01/2004	EXAMINER HUTSON, RICHARD G	
NORRIS, MCLAUGHLIN & MARCUS, PA 875 THIRD STREET 18TH FLOOR NEW YORK, NY 10022			ART UNIT 1652	PAPER NUMBER

DATE MAILED: 11/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/014,099

Applicant(s)

KUHN ET AL.

Examiner

Richard G. Hutson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 September 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 21-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The art unit location of your application and examiner has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1652, Examiner Richard Hutson Ph.D.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-20 in the paper of 9/14/2004, is acknowledged. The traversal is on the ground(s) that examination of all seven groups would not present a serious burden on the examiner. Applicants submit that even though the examiner has separately classified groups I-VII, the search burden issue has not been addressed in any respect. Applicants point out that groups I, III, IV and VI are still in the same class. Applicants argument in full has been completely considered, however found nonpersuasive because the search burden involved is based upon the number of additional subclasses that would need to be searched to additionally search the inventions of the other groups. For example, search of Group II would require search of subclass 536/23.4 and search of Group III would require search of subclass 435/462. A search of each of these subclasses would be unnecessary the search of the elected group I.

With respect to applicants argument that the claims of groups III and VI should at the very least be examined together with group I, applicants comments regarding the "rejoinder" of the groups drawn to methods of use of the product of group I are acknowledged and will be further dealt with at the time of determination of an allowable product of group I.

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The requirement is still deemed proper and is therefore made FINAL.

Claims 21-34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in the paper of 9/14/2004.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Currently no information disclosure statements are located in this application file.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: The following portions of the specification list sequences which appear to meet the definition for a amino acid sequence, but do not have an associated SEQ ID No: Figure 6 and 7.

Applicants attention is directed to the MPEP Section **2422.02**,

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The Requirement for Exclusive Conformance; Sequences Presented in Drawing Figures...It should be noted, though, that when a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings.

Appropriate correction is required.

Claim Objections

Claims 11, 15 and 18 are objected to because of the following informalities:

Claim 11 has a comma following the claim as opposed to a period.

Claim 15 recites "...any one of SEQ ID NOs:24...". It is suggested that this be amended to "...any one of SEQ ID NOs:24..." (space inserted between "f" and "S").

Claim 18 is missing a period at the end of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (2-20 dependent on) is indefinite in that it is confusing in the recitation "... having a recombinase activity similar to that of the corresponding wild-type

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recombinase...". Specifically applicants reference to "a recombinant activity" is confusing because it is unclear what "recombinase activities" applicants might be referring to in addition to "recombinase activity" itself. Applicants reference to "a recombinase activity" is confusing because use of "a" suggests that there may be more than one "recombinase activity". As such it is confusing which "recombinase activity" applicants are referring to. It is suggested that applicants either amend the claim to correct this, such as deleting "a" from the recitation or explain. In the interest of advancing prosecution, the claim has been interpreted as "... having recombinase activity similar to that of the corresponding wild-type recombinase..."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 9-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5 and 9-19 are directed to all possible fusion proteins comprising a recombinase protein or mutant thereof having recombinase activity and a signal peptide linked to said recombinase domain. The specification, however, only provides the representative species of SEQ ID NO: 23, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single

disclosed species. The specification also fails to describe additional representative species of these fusion proteins by any identifying structural characteristics or properties, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 2 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the fusion protein of comprising a recombinase domain and a signal peptide linked to said recombinase, wherein said fusion protein comprises the amino acid sequence of SEQ ID NO: 23, does not reasonably provide enablement for a fusion protein comprising a recombinase domain and a signal peptide linked to said recombinase, wherein the activity of the fusion protein in eukaryotic cells is significantly higher as compared to that of the wild-type recombinase.³ The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 2 and 5 are drawn to the fusion proteins of claim 1, wherein said recombinase protein or mutant thereof has a recombinase activity significantly higher than or similar to that of the corresponding wild-type recombinase protein.

The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the claimed fusion proteins. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated by a protein amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. For example as pointed out by applicants specification on page 6, lines 21-30, the association of any signal peptide NLS with any recombinase does not necessarily lead to an enhancement in the recombination efficiency. However, in this case the disclosure is limited to that fusion protein having the amino acid sequence of SEQ ID NO: 23.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any fusion protein comprising a recombinase domain and a NLS signal peptide wherein said fusion protein maintains or has an increase in the recombinase activity relative to the wild-type recombinase because the specification does not establish: (A) those recombinase proteins which may be so modified resulting in the desired maintenance or increase in activity; (B) the general tolerance of recombinases to such modification and extent of such tolerance; and (C) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which those fusion proteins which would result in the desired effect and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (See Le et al., *Nucleic Acids Research*, Vol. 27, No. 24, pp 4703-4709, 1999 and Schwikardi et al., *FEBS Letters*, Vol 471, pp 147-150,

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2000), Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those fusion proteins of the claimed genus having the claimed activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including those claimed fusion proteins which have a maintenance or increase in the recombinase activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9, 10-13, 17, are rejected under 35 U.S.C. 102(a) as being anticipated by Schwikardi et al. (FEBS Letters, Vol 471, pp 147-150, 2000).

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Schwikardi et al. teach a fusion protein comprising a recombinase domain comprising a recombinase protein or a mutant thereof, specifically the Cre recombinase, and a signal peptide domain, derived from the SV40 NLS, which directs nuclear import of said fusion protein in encaryotic cells.

Claims 1-5, 9, 10-13, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Le et al. (Nucleic Acids Research, Vol. 27, No. 24, pp 4703-4709, 1999).

Le et al. teach a fusion protein comprising a recombinase domain comprising a recombinase protein or a mutant thereof, specifically the Cre recombinase, and a signal peptide domain, derived from the SV40 NLS, which directs nuclear import of said fusion protein in encaryotic cells.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax

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phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Richard G. Hutson', with a long horizontal flourish extending to the right.

Richard G Hutson, Ph.D.
Primary Examiner
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rg
10/26/2004